

REMARKS

Request for Examiner Interview

Applicants respectfully request an interview with the Examiner. In this respect, Applicants respectfully request the Examiner to kindly contact the undersigned attorney to arrange a time for the interview.

The Present Invention

The present invention pertains to methods for cell release and mobilization comprising administration of hyaluronan (HA).

The Pending Claims

Claims 171-204 are pending currently. All of the pending claims are directed to methods for releasing or mobilizing cells using a form of hyaluronic acid. Reconsideration of the pending claims is respectfully requested.

Summary of the Office Action

The Office has rejected claims 111, 114, 115, and 136 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Claims 103, 106-111, 114-126, 130-136, 138, 139, 141, 143, and 144 stand again rejected under 35 U.S.C. § 103(a) as obvious over Hamann et al. (i.e., *The Journal of Immunology*, **1995**, 154, 4073-4080) in view of Falk et al. (i.e., U.S. Patent 5,827,834).

Discussion of Amendments to the Claims

Claims 103, 106-111, 114-126, 130-136, 138, 139, 141, 143, and 144 have been cancelled. New claims 171-204 have been added.

Specifically new claim 171 is similar to original claim 103, but it recites a method of releasing cells from bone marrow and other tissue of a patient into blood of the patient. New dependent claims 172, 173, 176 and 177 track original claims 114, 108, and 130. New dependent claims 174 and 175 recite that the molecular weight of the form of hyaluronic acid is 200,000 to 300,000 daltons and 25,000 to 100,000 daltons, respectively. Support for claim 174 can be found in the specification at page 23, line 1. Support for claim 175 can be found in the specification at page 23, line 9-11 which recites the ranges of 25,000 to 50,000 daltons and 50,000 to 100,000 daltons.

New claim 178 is the same as original claim 103, except that it recites that the molecular weight of the form of hyaluronic acid is 25,000 to 100,000 daltons, thereby incorporating the feature of new claim 175. New dependent claims 179 and 180 recite features from original claims 106 and 108.

New claim 181 is similar to original claim 116, but it recites a plurality of dosages comprising (a) a priming dosage of a form of hyaluronic acid in an amount of less than about 3 mg/kg patient body weight, and (b) one or more additional dosages of a form of hyaluronic acid in an amount of at least about 1.5 mg/kg patient body weight. As such, new claim 181 combines features of original claims 106, 116, 122, and 123. New dependent claims 182-185 incorporate the features recited in original claims 117, 118, 119, 120, and 121. New dependent claims 186 and 187 recite a method of administration wherein "the priming dosage is in the amount of 1.5 mg/kg patient body weight" and "additional dosages comprising 3mg/kg patient body weight, 6 mg/kg patient body weight, and 12 mg/kg patient body weight are administered to the patient following weekly intervals." Support for claims 186 and 187 can be found in the specification, for example, on page 22, lines 2-7.

New claim 188 is similar to original claim 125, but it recites a method of releasing cells comprising administering a dosage consisting essentially of a form of hyaluronic acid. New dependent claims 189-194 are identical to claims 172-177 discussed above.

New claim 195 is similar to original claim 126 except that it recites a method of transplanting stem cells into a patient comprising the steps of administering hyaluronic acid to a donor, harvesting stem cells from blood of the donor, and transplanting stem cells into the patient. Support for claim 195 can be found in the specification at page 24, line 20, through page 25, line 27. New dependent claims 196 and 197 recite that the patient is either the same as the individual or is different than the individual. Support for claims 196 and 197 can be found in the specification at page 24, lines 22-24 which states that the transplantation can be autologous (i.e., donor = patient) or allogenic (i.e., donor \neq patient).

New claim 198 is the same as original claim 131 except that it recites a method of treating allergy or asthma comprising administering to a patient showing symptoms of allergy or asthma a form of hyaluronic acid. New claim 199 is similar to original claim 132, but it recites a method of treating a patient having low levels of

red blood cells comprising administering to the patient a form of hyaluronic acid. New claim 200 is similar to original claim 138, but it recites a method of harvesting tissue for organ transplantation comprising administering to a patient in need of an organ transplant a form of hyaluronic acid. New claim 201 is similar to original claim 139, but it recites a method of mobilizing cells in an *ex vivo* organ comprising providing an *ex vivo* organ that has been harvested from a patient and infusing a form of hyaluronic acid into the *ex vivo* organ. New claim 202 is similar to original claim 141, but it recites a method of treating organ rejection comprising infusing into a patient showing signs of immunologic rejection of an organ graft a form of hyaluronic acid. Thus, claims 126, 131, 132, 138, 139, and 141 are rewritten as claims 195, and 198-202.

New claim 203 recites a method of treating a patient needing an increase in the number of stem cells in peripheral blood comprising administering hyaluronic acid. New claim 204 recites a method of increasing the number of stem cells in the blood of a patient comprising administering hyaluronic acid. Support for new claims 203 and 204 can be found in the specification, for example, at page 31, lines 11-37.

No new matter has been added by way of any of these new claims.

Discussion of the Indefiniteness Rejections

The Office has rejected claims 111, 114, 115, and 136 as being indefinite under 35 U.S.C. § 112, second paragraph. These rejections are moot in view of the cancellation of those claims. The rewritten claims have addressed and overcome the indefiniteness rejections. Since all of the pending claims satisfy the requirements of 35 U.S.C. § 112, the rejections thereunder should be withdrawn.

Discussion of the Obviousness Rejection

The obviousness rejection of claims 103, 106-111, 114-126, 130-136, 138, 139, 141, 143, and 144 over Hamman et al. and Falk et al. is moot in view of the cancellation of those claims. The newly added claims are non-obvious for the reasons discussed below.

The Hamann Reference

Hamann does not teach or reasonably suggest administering hyaluronic acid to release or mobilize cells in a patient. While Hamann shows that in certain cell cultures the administration of hyaluronic acid leads to cell proliferation, Hamann fails to recognize the full activity of hyaluronic acid.

In particular, Hamann does not disclose or suggest that hyaluronic acid acts to (a) induce de-adhesion of the cells from their anchored positions and (b) induce the movement of those cells away from the tissue in which they were produced and anchored (e.g., the bone marrow) and into another part of the body of the patient (e.g., the blood stream). It is to be noted that cell de-adhesion and organized movement of those cells to a different site is not dependent on, nor is it a natural consequence of, cell proliferation. In fact, cell proliferation requires a functional anchorage and the proliferated cells, if inappropriately detached from that functional anchorage, often undergo a death-directed anoikis process. Thus, if anything, the concept of cell proliferation is contrary to the idea of cell release or cell mobilization.

Moreover, even if the proliferated cells successfully detached from the anchorage and avoided anoikis, those cells would still be unable to relocate, for example, from the bone marrow to the circulatory system. Rather, the detached cells would float or diffuse passively within the tissue and would be unable to effectively navigate the various tissue barriers (e.g., stromal cells, endothelial cells, basement membranes, or extra cellular matrix).

The Falk Reference

Falk discloses *in vivo* administration of hyaluronic acid having a molecular weight of 150,000 to 750,000 daltons; however, Falk does not disclose or even recognize the ability to promote cell release or mobilization by administering hyaluronic acid. In distinct contrast, Falk discloses the use of hyaluronic acid as a penetration enhancer. Specifically, Falk suggests administration of a medicinal and/or therapeutic agent to treat a disease or condition with a sufficient amount of hyaluronic acid to facilitate the agent's penetration through the tissue (col. 10, Summary of the Invention). Falk refers to the role of hyaluronic acid in the "facilitation of the delivery of transport of a chemical to a site in a mammal" (col., 13, lines 65-67).

Moreover, Falk neither discloses nor suggests dosage levels or administration regimens appropriate for the administration of hyaluronic acid itself as an active ingredient. Rather, Falk discloses appropriate dosage amounts and regimens for administration of hyaluronic acid as a *carrier* in combination with other active therapeutic drugs. In fact, Falk fails to even recognize that hyaluronic acid itself may be used as a therapeutic agent for treating diseases or conditions. Thus, one of ordinary skill in the art would not be motivated to apply the dosage levels of hyaluronic acid taught by Falk for *in vivo* combination drug treatments to methods directed at promoting cell release and mobilization.

Claims 171-177

Neither Hamann nor Falk discloses or reasonably suggests a method of releasing cells from bone marrow or other tissues of a patient comprising administering hyaluronic acid. As discussed above, Hamann fails to teach or even recognize the ability of hyaluronic acid to promote de-adhesion of cells and/or relocation of such cells across tissue barriers. Falk teaches the use of hyaluronic acid as merely a penetration enhancer for other therapeutic agents and thus, also fails to teach or recognize the ability of hyaluronic acid to promote de-adhesion and/or relocation of cells. In fact, Falk fails to even recognize that hyaluronic acid has any therapeutic benefit at all when administered to a patient. Thus, the cited references, either alone or in combination, fail to anticipate or render obvious the invention recited in the newly added claims 171-177.

Claims 178-180

Neither Hamann nor Falk discloses or reasonably suggests the use of hyaluronic acid having a molecular weight of 25,000 to 100,000 daltons. Hamann provides no teaching at all regarding the molecular weight of hyaluronic acid. Falk teaches away from the claimed range by suggesting the use of hyaluronic acid having a molecular weight of less than 750,000 and greater than 150,000 daltons (see, e.g., claim 1). Thus, the cited references, either alone or in combination, fail to anticipate or render obvious the invention recited in the newly added claims.

Claims 181-187

Neither Hamann nor Falk discloses or reasonably suggests a method of releasing cells comprising administering to a patient a plurality of dosages as recited in pending claims 181-187. In particular, neither reference teaches the administration of a priming dosage having an amount of less than about 3 mg/kg patient body weight followed by the administration of one or more additional dosages of hyaluronic acid having an amount of at least about 1.5 mg/kg patient body weight. Hamann provides no teaching at all regarding dosage amounts or dosing regimens for *in vivo* administration. Falk is directed to the use of hyaluronic acid as a penetration enhancer for the administration of other therapeutic agents. Thus, one of ordinary skill in the art would not be motivated to apply the combination dosage amounts and dosage regimens described in Falk to the method for promoting cell release from bone marrow recited in the pending claims. Even if the teachings of Falk were applied to the claimed method of releasing cells, Falk does not disclose the administration of a priming dosage of less than about 3 mg/kg followed by additional dosages of at least about 1.5 mg/kg as recited in the pending claims. Thus, the cited references, either alone or in combination, fail to anticipate or render obvious the invention recited in the newly added claims.

Claims 188-194

Neither Hamann nor Falk discloses or reasonably suggests administration of a dosage "consisting essentially of" hyaluronic acid to a patient for promoting the release or mobilization of cells from bone marrow or other tissues. As discussed above, Hamann fails to teach or even recognize the ability of hyaluronic acid to promote de-adhesion of cells and/or relocation of such cells across tissue barriers. Falk *only teaches the use of hyaluronic acid in combination with other therapeutic agents* and does not recognize that hyaluronic acid itself could produce any therapeutic effect. Thus, the cited references, either alone or in combination, fail to anticipate or render obvious the invention recited in the newly added claims 188-194.

Claims 195-202

Neither Hamann nor Falk discloses the administration of hyaluronic acid to patients for any of the conditions recited by the pending claims. Specifically, the

cited references do not disclose or reasonably suggest a method for transplanting stem cells, method for treating allergy or asthma, a method for treating patients with low red blood cell levels, a method for harvesting tissue for organ transplantation, a method for mobilizing cells in an *ex vivo* organ, or a method for treating organ rejection as recited in claims 195, 198, 199, 200, 201, and 202.

Hamann does not disclose or suggest *in vivo* administration of hyaluronic acid and does not suggest the use of hyaluronic acid as a therapeutic agent for any particular disease or condition. Falk is directed to the use of hyaluronic acid as a penetration enhancer in combination with a variety of therapeutic agents. Falk does not disclose the use of hyaluronic acid for any of the diseases or conditions recited in the pending claims 195-202. Thus, the cited references, either alone or in combination, fail to anticipate or render obvious the invention recited in the newly added claims.

Claim 203 and 204

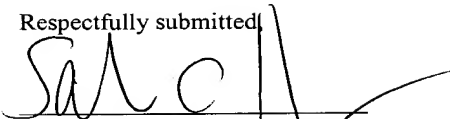
Neither Hamann nor Falk discloses a method of increasing the number of stem cells in peripheral blood of a patient or a method of treating a patient in need of an increase in the number of stem cells in peripheral blood comprising administering hyaluronic acid to the patient. Hamann discloses proliferation of cells but does not teach or suggest release and/or mobilization of those cells. Moreover, Hamann does not teach or suggest the use of hyaluronic acid in a method of treatment. Falk only discloses the administration of hyaluronic acid to enhance the penetration of other therapeutic agents. Falk does not teach or suggest that hyaluronic acid will increase the number of stem cells in the blood of a patient. Thus, the cited references, either alone or in combination, fail to anticipate or render obvious the invention recited in the newly added claims 203 and 204.

Conclusion

The application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

In re Application of Pilarski
U.S. Application No. 09/142,557

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Salim A. Hasan", written over a horizontal line.

Salim A. Hasan, Reg. No. 38,175
One of the Attorneys for Applicant
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson
Chicago, Illinois 60601-6780
(312) 616-5600 (telephone)
(312) 616-5700 (facsimile)

Date: March 13, 2002